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Dendritic Cell Therapy in Transplantation, Phenotype Governs Destination and Function

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While pharmacological methods are the mainstay for transplant immunosuppression, cell-based therapies are being increasingly studied as a potential alternative. Currently available immunosuppressive medications lack specificity leaving transplant recipients vulnerable to infection, malignancy, and drug related toxicities while still being susceptible to chronic rejection. *Donor-specific* tolerance would be clearly superior to global immunosuppression yet remains an elusive goal. Recent advances in cell-based therapies along with an improved understanding of central and peripheral tolerance mechanisms offer new possibilities for donor-specific immunomodulation. Amongst the many types of cell-based therapies tested to date some of the most successful thus far have involved donor stem cell transplantation in living-donor kidney transplant recipients[1]. However, the need ex vivo cell manipulation along with T cell depletion and bone marrow conditioning makes these methods arduous for many transplant recipients, and impractical for those receiving deceased donor organs. As an alternative cellular therapy, dendritic cells (DCs) are particularly attractive because of their role as central regulators of immune responses[2].

In this edition of *Transplantation*, Dr. Rosen and colleagues[3] present a comprehensive review of the role DCs play in producing allograft tolerance, highlighting recent studies demonstrating the utility of recipient-derived DCs loaded with donor antigen, rather than donor-derived DCs for transplant immunotherapy. Recipient-derived DCs present donor antigen in the context of self-MHC (indirect presentation), which in the setting of transplantation produces stronger allospecific effector responses when compared to direct presentation of donor MHC.[4] Thus autologous DCs are attractive as they also generate potent regulatory T cell responses when compared to suppressive macrophages or myeloid derived suppressor cells.[5] Murine models of allotransplantation demonstrate that these effects further extend graft survival with minimal pharmacologic immunosuppression.[6,7,8] Self-DCs may also be easier to maintain in an immature phenotype after transfer as they will not themselves be targeted by pathways of direct antigen presentation that can lead to their elimination or, even worse, induce their maturation and sensitize the recipient against donor antigen.

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As illustrated in the review by Rosen et al, the surface phenotype and location of DCs influence their effects on the immune system. Considered to be the most potent of the antigen presenting cell types, DCs are highly mobile sentinels of the innate immune system that collect peripheral antigens and present them to the adaptive immune system. The context in which DCs present antigen is regulated by a complex array of stimulatory and inhibitory signals that orchestrate the direction and magnitude of the immune response. In the presence of local inflammatory signals, tissue resident DCs mature (mDCs) and express increased levels of antigen presenting molecules, costimulation molecules, and inflammatory cytokines that differentiate T cells into effector phenotypes. In the absence of inflammation, immature DCs (imDCs) including migratory conventional DCs (SIRPα^+, CD11c$^+$, B220^{neg}) and plasmacytoid DCs (PDCA-1$^+$, CD11c$^+$, B220$^+$) with decreased antigen presenting potential, help maintain self-tolerance to peripheral antigens.

While the migratory routes of DCs are incompletely understood, there is evidence that their phenotype governs their destination and ultimately their function in regulating immune responses (Figure 1). In the setting of inflammatory signals, mDCs in the periphery also upregulate chemokine receptors (eg, CCR7 and CXCR4) and adhesion molecules (eg, LFA1). DCs expressing CCR7 and CXCR4 chemotaxis to LNs through attraction by their ligands (CCL21 and CCL19, and CXCL12, respectively) and LFA1/ICAM-1 interactions which are critical to DC adherence and residence in LNs where they stimulate and polarize T cells.[9,10] However, the roles of these molecules are complex and ‘semimature’ DCs expressing CCR7, yet low levels of CD40 and B7 have been found to have a role in steady state migration of skin DCs even in the absence of inflammation.[11]

As discussed by Rosen et al, intrathymic imDCs can produce tolerogenic responses. In the absence of inflammation, imDCs that express CCR9 and CCR2, but have low levels of CCR7 and CXCR4, can bypass the lymph nodes en route to the central venous system. The circulating imDCs can then home to the thymus driven by CCR9/CCL25 interactions[12] and migrate into the thymus though processes involving VLA4 and its ligand VCAM-1[12,13]. While the thymus has mechanisms for maintaining self-tolerance through its intrinsic expression of peripheral self-antigens regulated by the autoimmune regulator (AIRE) protein[14], peripheral sampling of self-antigens by immature DCs provides a supplemental mechanism for maintaining tolerance to peripheral tissue antigens[15]. The question remains whether these tolerance mechanisms can translate into effective cellular therapies for clinical transplantation.

If DC localization and function is determined by phenotype, then methods of isolating and preparing recipient DCs with the appropriate markers is critical to determining their capacity for immune modulation. The studies presented in the review by Rosen et al demonstrate the potential for DC based tolerance induction. Although clearly demonstrated in murine models, further mechanistic understanding in the human immune system is needed to translate these concepts into clinical feasibility, whether they be for the purpose of immune-inhibition in transplantation and autoimmune disease, or immune-stimulation for tumor therapy.[16] Already the administration of autologous tolerogenic DC preparations are beginning to be testing in clinical trials for the treatment of autoimmune diseases[15], and for immunosuppressive therapy in the setting of living-donor renal transplantation in the

European ONE Study[17]. However additional questions remain that may further improve efficacy in the setting of transplantation. These include refining methods for induction and maintenance of imDCs including ex vivo versus in vivo manipulation, the source for donor antigen, the incorporation of induction protocols, timing of therapy, and the durability of such cell-based treatments. As the marshals of the adaptive immune system, DCs hold significant potential for cell-based immune therapies. Further clinical studies will be required to determine if these concepts and methods can effectively translate to the human immune system which can vary greatly between individuals based on their immunologic history and physiology.

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Abbreviations

AIRE	Autoimmune regulator
CCR7	C-C chemokine receptor type 7
CCR9	C-C chemokine receptor type 9
CCL19	C-C motif chemokine ligand 19
CCL21	C-C motif chemokine ligand 21
CCL25	C-C motif chemokine ligand 25
CXCL12	C-X-C motif chemokine ligand 12
CXCR4	C-X-C chemokine receptor type 4
DC	Dendritic cell
ICAM-1	Intercellular adhesion molecule 1
imDC	Immature dendritic cell
mDC	Mature dendritic cell
LFA1	Lymphocyte function-associated antigen 1
MHC	Major histocompatibility complex
VCAM-1	Vascular cell adhesion molecule 1
VLA4	Very late antigen 4

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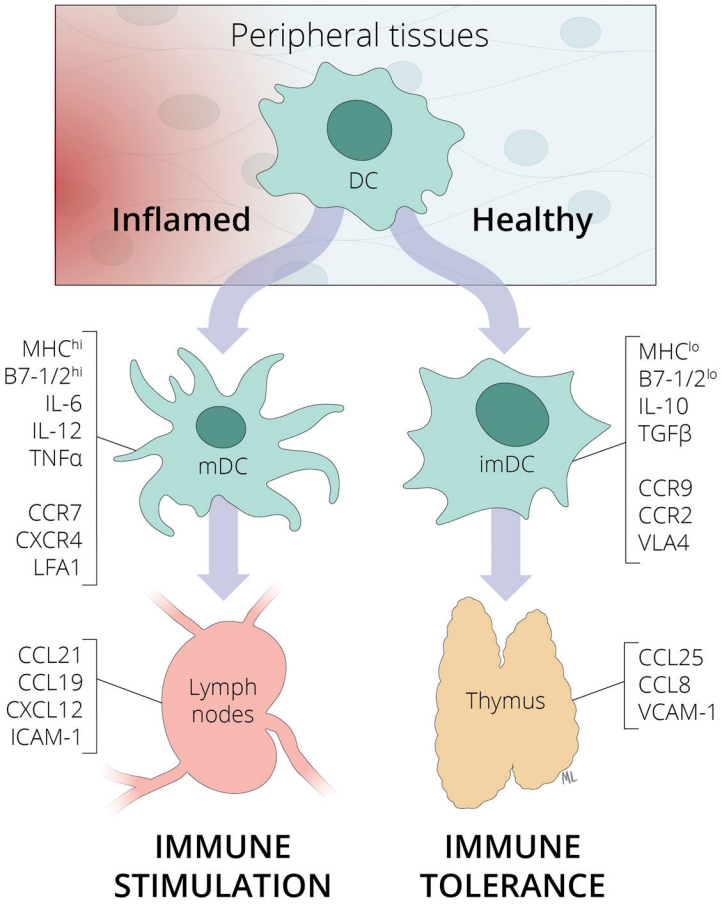

Figure 1. Dendritic cell phenotype governs localization and function

Inflammatory signals in peripheral tissues cause DC activation and maturation into mDCs. Based on the upregulation of specific chemokine receptors and adhesion molecules, mDCs traffic to lymph nodes and promote immune stimulation. Circulating from healthy peripheral tissues, imDCs can bypass lymph nodes and migrate to the thymus and promote immune tolerance to peripheral antigen. Illustrated by Megan Llewellyn, MSMI; copyright Duke University; with permission under a CC BY-ND 4.0 license